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(54) **Biologically active topical collagen support matrix: cosmetic and pharmaceutical uses and a process for its preparation.**

(57) A spongy and felt-like support material, consisting of an insoluble and soluble collagen matrix, is used as a 1) cosmetic carrier for the application of moisturizing collagen to the skin, or 2) as a pharmaceutical carrier for the application of topically efficacious therapeutics.

A process for its preparation is described.

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Sp. 4, 2: 40 - 62
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Description

"Biologically active topical collagen support matrix: cosmetic and pharmaceutical uses and a proc ss for its preparation"

This invention describes a support matrix for cosmetic or pharmaceutical use consisting of collagen which is partially naturally reticulated and insoluble and partially water soluble. When brought into contact with the skin, this support matrix has the property of transferring into the skin a considerable quantity of water from the insensible perspiration of the skin. This support matrix is therefore suitable for use in the treatment of dry skin and for facilitating the penetration of active substances into the skin.

Collagen is a well known constituent of white fibrous tissue in animals. It is found in bone, cartilage and tendons, but particularly in connective tissue. Methods for extracting collagen from tissue are well known.

The aim of the present invention is to produce from natural collagen (prepared using known methods) a biologically active support consisting of collagen which can release, both in aqueous solution and in contact with the skin, from 0.5% to 50% of its weight in natural soluble animal collagen. Such a support must have a denaturation temperature no lower than 37° C. Although this support is a new product, it has known cosmetological activity (as described below).

However, it does have novel aspects. It may be used for incorporation of cosmetically or pharmacologically active substances, with the advantage that the support may be stored with none of the denaturation or degradation problems encountered with similar known products.

The support matrix according to this invention, may be prepared in various forms (such as spheres, cylinders or sheets) which may due to its soft spongy or felt-like structure be cut into the size and thickness desired.

The presence of natural insoluble collagen, while not an active substance in itself, endows the support matrix with considerable firmness, facilitating handling during production and packaging as well as easy application and removal.

The product may be used for cosmetic or pharmacologic purposes by bringing suitable forms, eg: sheets, into contact with the desired area of the skin surface. The natural moisture of the skin then dissolves the soluble collagen and any other active substances, which can then exert their effects upon the skin.

While collagen support materials with a spongy or felt-like structure are already known, their denaturation temperature is too low, or they cannot release natural soluble collagen (either in aqueous solution or on contact with the skin) since they are produced using highly reticulated chemical binding substances. When treated with these chemicals, natural collagen is irreversibly reticulated so as to bind any natural soluble collagen almost completely. Furthermore, the presence of these binding or preservative substances is a contra-indication to their main cosmetic application of treatment of dry skin. They may, in fact, be quite damaging to the skin itself.

Attempts were made to solve this problem by using natural soluble collagen in oil/water emulsions, in aqueous or glycol solutions, or in other chemico-physical forms to the used either directly on the skin or by application on a reticulated collagen support at the moment of use. However these products suffer from the severe disadvantage that collagen in solutions or emulsions has an extremely brief and often indeterminant life cycle due to its rapid denaturation. Therefore, the use of preservatives is required and efficacy is even then not reliable.

The following publications described the techniques discussed above:

K. H. Stenzel, T. Miyata, A. L. Rubin,
Collagen as biomaterial
Ann. Rev. Biophys. Bioeng., 3,231-253 (1974);
U.S.A. patent 3,823,212;
German patent 2625289;
A. Berg, H. Lindner,
Schutz-Proteine in der Kosmetik
Parf. & Kosm., 60, 74-78 (1979);
U.S.A patent 4,193,813;
A. Berg, H. Dieringer,
Collagen mask - Cosmetic Application & Analytical Control;
Atti Congresso Naz. SICC. Milano 24-25 Nov. 1983
M. Chvapil, Z. Eckmayer,
Role of proteins in cosmetics,
Int. Journal of Cos. Science, 7, 41-49 (1985)

The support matrix material, according to this invention, differs from previous collagen based materials in two ways:

First, it is charged with natural, soluble and stable collagen when it is packaged and it releases said collagen in high quantities on contact with the skin.

Second, since no preservatives or reticulating agents are used in the support material in this invention, there are none of the negative reactions which may ensue with similar previous products, such as irritation or rejection caused by trace residues of these preservatives or curing agents.

The advantages of this collagen support matrix material, according to the invention, are due above all to the fact that once the natural and soluble collagen is combined with the natural insoluble collagen (treated with no chemical reticulating agents) a final product is obtained which, when moistened or placed in contact with the skin, releases natural soluble collagen while the insoluble collagen fibers form a uniform, moist, semi-occlusive layer.

Thereby, action of the natural soluble collagen on the skin is facilitated, and the moisturizing process is enhances, as has been shown in many publications on previous techniques. (Riso, R. R.: Protein derivatives - Moisture and 'That look of youth'.

Aerosol Age. **14** 30 (1969); Riso, R. R.: Protein derivatives in cosmetics. Cosmet. Perfum. **89** 45-8 (1974); Nagelschmidt, M. and Struck, H.: Kollagen als Cosmeticum? Arch. Derm. Forsch. **250** 237-43 (1979); Richter, K.: Collagen (Losliches collagen contra unlosliches collagen). Information No. 328 in Richter, K. GmbH (Ed.) Chemisches Laboratorium (1971) (Adolph Furst & Sohn, Berlin); Tronnier, H.: Zur dermatologischen Wirksamkeit einer Kollagensalbe: Klinische-experimentelle Kurzmitteilung. Artzl. Kosmetologie **6** 93-5 (1976); Huc, A. et al.: Etude de la penetration in vivo dans la peau de rat du collagene acido-soluble en solution acide ou en melange dans une creme cosmetique. Inter. J. Cosmet. Sci. **3** 159-83 (1981); Todd, R. D.: Soluble collagen: new protein for cosmetics. Drug Cosmet. Indust. **117** 50-2, 56, 134-38 (1975); Groher, B.: Losliches Kollagen in kosmetischen Preparaten. Seifen Ole Fette Wachse **102** 499-500 (1976); Johnsen, V. L.: Proteins in cosmetics and toiletries. Drug Cosmet. Indust. **126** 36-9, 136 (1980).)

Another advantage is that in the dry state the support material may be stored with no addition of presevatives; in fact it may be sterilized with gamma radiation if suitably packaged. This sterilization is impossible with natural soluble collagen incorporated in emulsions or aqueous solutions. In fact, according to the invention, the natural soluble collagen in the support matrix remains stable for long periods, eve at high ambient room temperatures. This stability cannot be assured for products in aqueous solutions.

There are no other cosmetic products based on soluble collagen (such as emulsions, or aqueous or glycol solutions) which offer the guaranteed availability of such a high concentration of natural soluble collagen, with its inherent chemico-physical behaviour which allows complexation with other components and also stability

Furthermore, the possibility of incorporating in the collagen matrix other cosmetically or pharmacologically active substances gives rise to the possibility of a product for local application to the skin which in addition to its moisturizing effects may also show therapeutic activity.

Therefore, one object of the present invention is a biologically active support matrix consisting of natural animal collagen wherein said matrix contains water-insoluble reticulated collagen as well as a quantity of 4.0% to 50% by weight of natural, water-soluble non-reticulated collagen, with a denaturation temperature higher than 37° C which may be dissolved in the presence of water.

Another object of the present invention is a process for the preparation of said support, consisting of the following operations:

- dissolving in distilled and/or sterilized water at room temperature a quantity of enriched natural soluble collagen prepared using known methods from biological tissue of young mammals, so as to obtain a solution with a concentration of from 5.0% to 40% by weight of collagen which does not degrade at temperatures below 37° C.
- addition of a quantity of insoluble collagen to the solution in a proportion ranging from 0.5:1 to 1:0.5 with respect to the soluble collagen, stirring to obtain a homogeneous mixture.
- rapid cooling of said mixture with stirring down to a temperature between 0° C and -5° C, so as to obtain a pourable mixture to be placed in forms for lyophilation.
- Lyophilation in said forms.

The invention is described below in greater detail in one preferred embodiment.

The support matrix, according to the invention, is prepared from a starting material consisting of concentrated natural and soluble animal collagen, obtained in successive separation and purification operations from biological tissue from young mammals, by means of acid extraction. This extraction process is already known. (Chvapil, M.: Process for the production of collagen fiber fabrics in the form of felt-like membranes or sponge-like layers - U.S. Patent 3. 823,212.9 (July 1974); Ries, P.E., Reinach: Verfahren zur Herstellung eines sterilen Kollagenproduktes mit filz- bzw. vliesartiger Faserstruktur. BRD Patent 2625289 (June 1976))

It should be noted that the denaturation temperature of collagen depends on the starting material used for extraction of the collagen itself. The starting material should therefore be selected on the basis of known criteria so that the collagen has a denaturation temperature higher than 37° C when it is prepared, preferably between 39° C and 45° C. Collagen denaturation, however, does not depend on temperature alone but on other factors as well, such as the presence of chemical substances.

Therefore, according to the present invention, the stable storage capacity of the soluble collagen does not depend directly on the natural denaturation temperature established by the choice of starting material, as mentioned above, but on the characteristics of the production process and material so obtained, unlike similar known products.

The preferred starting material for the soluble collagen is fresh tissue from young mammals, preferably in enriched solutions.

According to the invention, said mammalian source is dissolved in cold distilled and/or sterilized water, so as to achieve a solution with a concentration of active substance between 5.0% and 40% by weight with respect to the total solution. The solution is checked analytically to ensure that its denaturation temperature is not below 37° C.

The solution is preferably filtered to eliminate any impurities and the filtered solution is then treated with a homogenous suspension of insoluble animal collagen fibres, prepared using known methods. (Stenzel K.H., Miyata T., Rubin A. L.: Collagen as Biomaterial. Ann. Rev. Biophys. Bioeng. **3** 231-253 (1974); Chvapil, M.: Process for the production of collagen fiber fabrics in the form of felt-like membranes or sponge-like layers - U.S. Patent 3. 823,212.9 (July 1974); Ries, P.E., Reinach: Verfahren zur Herstellung eines sterilen Kollagenproduktes mit filz- bzw. vliesartiger Faserstruktur. BRD Patent 2625289 (June 1976))

The mixture is then stirred to ensure homogeneity and rapidly cooled, using refrigeration machines known in the cosmetic or pharmaceutical field for

similar purpose.

The temperature is lowered until ice crystals form (between 0° C and -5° C) and the mixture is stirred so that the ice crystals are as finely divided as possibl throughout the mixture. The mass must b sufficiently fluid to be poured into forms which serve to give the final shape to the support matrix material. The form selected is a function of the particular application for which the support matrix is to be used, as is evident to an expert in the field. The forms are then inserted in a lyophilation apparatus, in which the material is brought to its final appearance.

In this way the finished biologically active support matrix has an appearance that ranges from spongy to felt-like, and has the ability to release (in the presence of moisture) a quantity of from 0.5 to 50% of its weight as natural soluble collagen.

The support matrix, according to the invention, may be used as such for treatment of dry skin, since soluble collagen is known to produce a moisturizing effect, while the matrix containing the insoluble collagen acts as carrier and also as an occlusive wall to prevent dispersion of the active substance.

One important aspect of the present invention is that it is possible, during the soluble collagen solution phase or during the addition of insoluble collagen, to introduce cosmetically or pharmacologically active substances which are then readily released together with the soluble part of the collagen.

These active substances may be antibiotics, chemotherapeutics, antiseptics, cortisones, or any other active principle used pharmaceutically, biologically or cosmetically. Thus, the possibilities of utilization of the biologically active support matrix, according to the invention, are greatly enhanced. In the way, local treatment of both healthy skin (cosmetic treatment) and of unhealthy skin is possible, as is clear to an expert in this field.

Furthermore, the optimal storage properties of the product allow any active substances to be used in relatively low concentrations, resulting in savings in terms of costs.

It is clear that modifications or variations may be made to the support matrix, according to the invention, without going beyond the bounds of the invention itself.

Claims

1. A biologically active support matrix which is spongy or felt-like in appearance comprising a natural animal collagen matrix, wherein said matrix contains water-insoluble reticulated collagen as well as a quantity of 4% to 50% by weight of natural, water-soluble non-reticulated collagen, with a denaturation temperature above 37° C which may be dissolved in the presence of water.

2. A support matrix, according to claim 1, also containing cosmetically and/or pharmacologically active substances.

3. A process for the preparation of the support matrix as recited in claim 1, comprising operations of:
- dissolving in distilled and/or sterilized water at room temp rature a quantity of enriched natural soluble collagen prepared using known methods from biological tissue of young mammals, so as to obtain a solution with a concentration of from 5% to 40% by weight of collagen which does not degrade at temperatures below 37° C.;
- addition of a quantity of insoluble collagen to the solution in a proportion ranging from 0.5:1 to 1:0.5 with respect to the soluble collagen, stirring to obtain a homogeneous mixture;
- rapid cooling of said mixture with stirring down to a temperature between 0° C and -5° C, so as to obtain a pourable mixture to be placed in forms for lyophilation;
- lyophilation in said forms.

4. A process according to claim 3, wherein the soluble collagen solution is filtered to remove any impurities before the addition of the insoluble collagen.

5. A process for the preparation of the support matrix as recited in claim 2, wherein cosmetically or pharmacologically active substances are added during the solution of the soluble collagen and/or during the addition of the insoluble collagen.